Case Reports

Reye's Syndrome in an Adult Patient

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REYE'S SYNDROME is a relatively recently recognized clinical syndrome of rapid and sometimes catastrophic neurologic deterioration in pediatric patients, with associated hepatic dysfunction, elevated plasma ammonia and amino acid levels and a preexisting viral syndrome. In rare cases, this syndrome can occur in adults. We describe such a case in the oldest patient reported. Physicians treating older patients need to be aware of the possibility of the Reye's syndrome in this age group because prompt recognition and treatment are vital. Vigorous clinical support, reduction of increased intracranial pressure and prevention of secondary complications can salvage a functionally intact person from what can otherwise be a devastating neurologic catastrophe.

Report of a Case

The patient, a 59-year-old left-handed homemaker, noted the development of "flu"-like symptoms of sore throat and malaise about a week before hospital admission. Over the first two days she became progressively worse, noting body aches and nausea, although no fever. By the third day, the patient seemingly began to improve but this recovery was short-lived. On the fifth day following the onset of symptoms, she had severe nausea, intractable vomiting, generalized malaise and confusion. Though free from headaches, her downhill course, progressively increasing confusion and emerging belligerence led her family to bring her to the emergency room for evaluation seven days after her first symptoms.

On initial examination, she appeared well nourished and in her late middle age. She was confused, thrashing about on the emergency stretcher and unable to communicate. The patient's neck was supple without meningismus. General otolaryngologic and physical examinations revealed no focal sites of infection or other acute disease. Asterixis, or "liver flap," was not apparent. The skin of the back had a few small superficial pustules, consistent with a benign staphylococcal infection.

A complete neurologic examination on the evening of admission showed that the patient was extremely confused, disoriented and alternately stuporous and combative. She could be aroused with stimuli but was incoherent and incapable of following complex commands. Speech was sparse, garbled, inappropriate and only semi-intelligible. On serial cranial nerve testing, the discs were slightly hyperemic but she had no overt papilledema, no focal cranial nerve dysfunction and no focal deficits. She did not blink to visual threat. Motor testing showed no significant focal paresis or incoordination, although the patient was somewhat diffusely dyspraxic and disorganized in her motor movement. Symmetrically increased tone was noted. In addition, the patient occasionally swiped at her face with her right hand, as though hallucinating. Bilateral spontaneous extensor posturing was periodically observed. Sensation was intact to noxious stimuli only, as the patient could not cooperate for more definitive testing. Reflexes were normoactive and symmetric, but a bilaterally positive Babinski's response was noted.

The patient's family history was unremarkable. Review of her personal history showed that a probable early childhood case of polio resulted in a slight but permanent right hemiparesis, most prominent in the lower limb. A head injury two years before this evaluation resulted in a ten-minute loss of consciousness followed by complete recovery. Medicines taken periodically included aspirin, minor analgesics, estrogens, vitamins, proprietary diet preparations and penicillin, but the patient's family did not know for sure if she had recently taken any salicylates during this illness. The patient was free from allergies and bleeding problems.

Initial laboratory screening of blood and urine specimens gave normal values except for elevation of the hematocrit, plasma ammonia, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and lactic dehydrogenase (LDH) enzymes. The hematocrit was initially 58%, which probably represented hemoconcentration due to protracted emesis, superimposed on a normal altitudinal polyerythrocythemia (normal hematocrit is as much as 47% at this altitude of 1,372 m [4,500 ft]). The leukocyte count was 4,700 per μl on admission, peaked to 17,100 per μl after three days (patient was being given steroids also) and gradually fell thereafter. The ammonia level was initially 124 μg per dl, rose to 172 μg per dl in two days and fell to 14 μg per dl by the eighth hospital day. The serum ALT and AST levels were initially 551 and 483 units per ml, respectively, and gradually fell from those levels during her hospital stay. The LDH value was initially 546 units per liter and gradually fell thereafter. Creatine kinase, bilirubin and prothrombin time values were initially normal and remained normal or only minimally elevated. A routine chest x-ray film was unremarkable, as was an electrocardiogram. Findings on a computed tomographic (CT) scan of the brain were interpreted as within normal limits, without focal abnormalities except for mild and symmetric ventricular narrowing consistent with mild diffuse cerebral edema. Cerebral angiography did not show arteritis, occlusions, stenosis, tumors or other abnormalities. An electroencephalogram showed diffuse slowing consistent with metabolic encephalopathy.

The initial diagnosis was that of a diffuse metabolic or

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ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
AST = aspartate aminotransferase
CT = computed tomographic
LDH = lactic dehydrogenase

inflammatory encephalopathy. Coincident with her neurologic deterioration, the patient began suffering focal seizures and then generalized convulsions. They were initially refractory to intravenous administration of phenytoin, but finally responded to diazepam given intravenously, and were subsequently kept under control with phenytoin.

Further laboratory investigation showed a qualitative elevation of the serum glutamine and alanine levels on two-way thin-layer chromatography. A lumbar puncture showed normal pressure and clear, colorless spinal fluid. The cerebrospinal fluid protein was 3 mg per dl and the glucose was 80 mg per dl. There were 39 erythrocytes per μl and 1 leukocyte per μl. Routine cultures of the spinal fluid were negative. Both heavy metal and drug screens were negative. A liver biopsy was not done.

On the evening of admission the patient's condition deteriorated, becoming comatose and decerebrate. She was taken to the intensive care unit where she was placed in a 45-degree head-elevated position and was treated with diuretics, fluid restriction and methylprednisolone sodium succinate, 20 mg every six hours. An endotracheal tube was inserted and the patient was artificially ventilated after being given an initial dose of thiopental sodium. Her deep state of coma was such that she did not fight or "buck" the respirator, and no more thiopental was given after the first eight hours. The patient was hyperventilated to bring the partial arterial carbon dioxide pressure down to the 25 to 29 torr range. The fundi were carefully monitored and overt papilledema was noted to develop the day after admission. No hemorrhages or exudates were noted, but the disc margins were distinctly blurred. This then resolved over the subsequent 72 hours.

The patient began to wake up 48 hours after her intubation, and by the third day after admission she was following simple commands. This improvement in mental state corresponded directly with a fall in the plama ammonia level. The patient then followed a course of progressive neurologic improvement and the endotracheal tube was removed without problems five days after her admission to hospital. Careful examination at this time showed no focal neurologic deficits except for some distal weakness in the right lower limb (chronic) and mild mental confusion. Physical therapy and gait training was begun and the patient was walking with assistance by the seventh day after admission. She was discharged in good condition 21 days after admission, and subsequent examination in the office showed no neurologic deficits other than her chronic, postpolio right lower limb monoparesis. On clinical follow-up a year later she was generally healthy and neurologically unchanged.

Discussion

This syndrome of "encephalopathy and fatty degeneration of the viscera" was first described by Reye, Morgan and Baral in 1963[1] and is typically found in children younger than 15 years. Since the first known adult case was detected in 1975, however, other isolated and scattered cases of this syndrome have been identified in adults and treated with varying degrees of success.[2-7]

Pathologically, the hallmark of this disease is fatty infiltration of the liver and viscera in association with biochemical abnormalities of hepatic enzymes and metabolites.[8-12] Brain changes are confined to diffuse edema in association with mitochondrial abnormalities.[13]

Salicylates have been indicted in the cause of this disease, although the specific relationship and mechanism are unclear.[14,15] Warnings against the use of salicylates in children at risk have been publicized for two years and during this time the incidence of the Reye's syndrome seems to have dropped substantially.

Although the cause of the Reye's syndrome is still somewhat obscure, the clinical syndrome itself is relatively well defined.[16-20] It begins with a viral prodrome, commonly respiratory in nature but not infrequently gastrointestinal or cutaneous. Many viruses have been isolated from these cases, but influenza B and varicella are the most common. The Reye's syndrome may be seen in any month of the year, but most commonly occurs between December and March.[21] A number of patients have taken salicylates during the viral prodrome period and this may be a contributing factor, albeit controversial.[22] Coincident with a period of liver dysfunction, patients then become neurologically obtunded and may suffer seizures. Following a period of repetitive nausea and vomiting, they may rapidly decline neurologically, frequently in association with the seizures, which may be difficult to control. Prompt recognition of the increased intracranial pressure and treatment thereof frequently lead to neurologic recovery and salvage of a normal or at least a functional patient.[23]

The differential diagnosis of an acute encephalopathy in adults includes a plethora of diseases, but a logical screening process will usually lead to the correct diagnosis. A detailed history is vital in elucidating the typical prodrome of the Reye's syndrome and eliminating other disease processes, such as drug overdose, head injury or vascular accident. A careful physical and neurologic examination will help to rule out meningitis or focal cerebral disease. A negative CT scan, coupled with normal findings on cerebrospinal fluid examination (done *after* the CT scan has ruled out a mass lesion) will suggest a metabolic encephalopathy. The diagnostic algorithm then leads to a complete biochemical analysis of body fluids, especially serum, at which point the exact metabolic abnormality should be clear. In cases of the Reye's syndrome, the most consistent laboratory finding would be an elevated ammonia level, although more detailed analyses of hepatic enzymes and cytologic abnormalities of hepatic tissue specimens can sometimes be of additional help in securing an accurate diagnosis.

At age 59 this patient represents, to our knowledge, the oldest patient to have the Reye's syndrome. Her presentation was typical in most indices except for her late middle age. Vigorous treatment brought about gratifying restoration of neurologic function to preillness levels. In short, her case affirms the importance of physicians' alertness to the possibility of the Reye's syndrome in both children and adults and subsequent rapid treatment to avoid severe disability, coma or even death.

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Severe Ethylene Glycol Intoxication With Multisystem Failure

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SINCE ETHYLENE GLYCOL was originally synthesized at the turn of the century, many uses have been found for it, most notably as a primary component in commercial antifreeze.

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ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
CT = computed tomographic

Formerly felt to be a nontoxic compound and even used as a carrier for early medicinals, it has since been shown to be a potentially lethal agent.[1] Ingestion of a significant quantity (greater than 75 to 100 ml) has resulted in a variety of biochemical derangements and multisystem failure, the most impressive of which are a refractory anion gap metabolic acidosis, oliguric or anuric acute renal failure and central nervous system dysfunction ranging from mild intoxication to coma and death.[1,2] Traditional treatment has centered on ethanol infusions of 5 to 15 grams per hour, to maintain ethanol blood concentrations of 1,000 μg per ml, and hemodialysis.[3,4,5]

We recently treated a patient who had a massive overdose of ethylene glycol that had gone unrecognized for 12 hours. In addition to the expected acidosis, coma and renal failure, cerebral edema and bone marrow arrest developed. The patient was treated with ethanol infusion and hemodialysis. Despite a seven-day period of coma, eight days of anuric renal failure and two weeks of pancytopenia, the patient survived.

Report of a Case

The patient, a 36-year-old man with a history of schizophrenia and idiopathic seizures treated with phenytoin, presented to a community hospital with ataxia and nystagmus that were initially diagnosed as a phenytoin overdose. His neurologic state deteriorated to stage 4 coma six hours after admission. At that time he was found to have a severe anion gap metabolic acidosis, which was treated with sodium bicarbonate. Toxicology screen was positive for ethylene glycol and negative for ethanol. Twelve hours after admission, an ethanol infusion was begun, and the patient was transferred to University of Colorado Health Sciences Center for further management.

On examination on arrival, he was comatose with Kussmaul's respirations. His blood pressure was 168/100 mm of mercury, pulse 122 and temperature 37.5°C (99.5°F) rectally. Bilateral papilledema without hemorrhages was noted. The neck was supple, and results of chest and cardiac examinations were normal. On neurologic examination he had spontaneous respirations but no response to deep pain, and a flaccid quadriparesis was present.

Blood gas determination on admission while the patient was breathing room air showed a pH of 7.00, a partial carbon dioxide pressure of 9 torr, a partial oxygen pressure of 108 torr and a base excess of −27 mEq per liter. The following laboratory values were elicited: serum sodium 157, potassium 3.4, chloride 100 and bicarbonate 4 mEq per liter; urea nitrogen 24 and creatinine 3.3 mg per dl, and the anion gap 53 mEq per liter. Hematocrit was 49% and the leukocyte count was 35,000 per μl. Analysis of urine showed numerous erythrocytes without casts and large numbers of needle-shaped crystals. Ethanol and ethylene glycol levels were 540 μg per ml and 4,650 μg per ml, respectively.

The patient was admitted to the intensive care unit and treated with sodium bicarbonate and a bolus of 30 grams of ethanol, followed by an infusion of 10 grams per hour of ethanol given as a 10% weight-per-volume infusion in 5%